CDER New Drug Review: 2013 Update

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Housekeeping

- Data and analyses presented on the following slides are thought to be accurate, but in order to provide the most up-to-date information have not undergone the same thorough quality control as is performed for official FDA reports
- Many staff in CDER provided data, analyses, and PowerPoint expertise for this talk; their work behind the scenes makes me look good each year. Special thanks and acknowledgement to:
  - The Performance Analysis Staff in CDER's Office of Program and Strategic Analysis
  - Mike Lanthier in the Office of the Commissioner

Themes in new drug review for 2013

- Continuing resolution - the new normal
- PDUFA V; hold the additional resources
- FDASIA implementation; what new resources?
- The "Program" takes off
- Breakthroughs breaking out
- Sequestration bites
- Shutdown shuffle
- Patient-focused drug development refocused
- "Slow down?" in NME approvals – not really
- Despite challenges, new drug review program successes continue!!

Topics to be covered

- How is CDER doing with regard to meeting PDUFA goals?
- What are the trends in new drug approvals?
  - IND activity, NME submissions, and NME approvals
- Implementation of PDUFA V/FDASIA
  - "Program" for NME review
  - Breakthrough Therapy Designation Program
- Update on PMCs/PMRs

What about PDUFA Goals?

- FDA continues to take PDUFA goals very seriously
  - These are commitments that we made to Congress and the American public for how we will do our work
- FDA is meeting or exceeding nearly all PDUFA goals for application review
- We are working to implement the enhancements agreed to under PDUFA V to the best of our ability despite the impact of the continuing resolution, sequestration, and government shutdown
  - CDER has not received the additional resources negotiated as part of PDUFA V (proposed PDUFA increases ≅ sequestration cuts)
  - Our ability to meet some goals may be compromised by continued resource constraints and competing priorities

FY 2012 Cohort: CDER Review Performance

	FY 2012	
Submission Type	Number Filed	Performance (Current)
Priority NME NDAs/original BLAs	16	94%
Standard NME NDAs/original BLAs	25	100%
Priority NDAs/BLAs	24	96%
Standard NDAs/BLAs	97	97%
Class 1 NDA/BLA Resubmissions	5	100%
Class 2 NDA/BLA Resubmissions	32	100%
Priority Efficacy Supplements	38	100%
Standard Efficacy Supplements	101	97%
Class 1 Efficacy Resubmissions	3	100%
Class 2 Efficacy Resubmissions	17	82%
Prior Approval Mfg Supplements	623	90%
CBE Mfg Supplements	1159	92%

Data as of 9/30/2013

FY 2013 Cohort: CDER Review Performance

	FY 2013	
Submission Type	Number Filed	Performance (Potential)**
Priority NME NDAs/original BLAs	17	100%
Standard NME NDAs/original BLAs	30	100%
Priority non-NME NDAs*	9	100%
Standard non-NME NDAs*	72	100%
Class 1 NDA/BLA Resubmissions	9	100%
Class 2 NDA/BLA Resubmissions	37	100%
Priority Efficacy Supplements	26	100%
Standard Efficacy Supplements	95	97%
Class 1 Efficacy Resubmissions	1	100%
Class 2 Efficacy Resubmissions	7	86%
Prior Approval Mfg Supplements	630	93%
CBE Mfg Supplements	1130	97%

Data as of 9/30/2013

*Beginning in FY13, the new tracked metric is non-NME Priority and Standard NDAs.

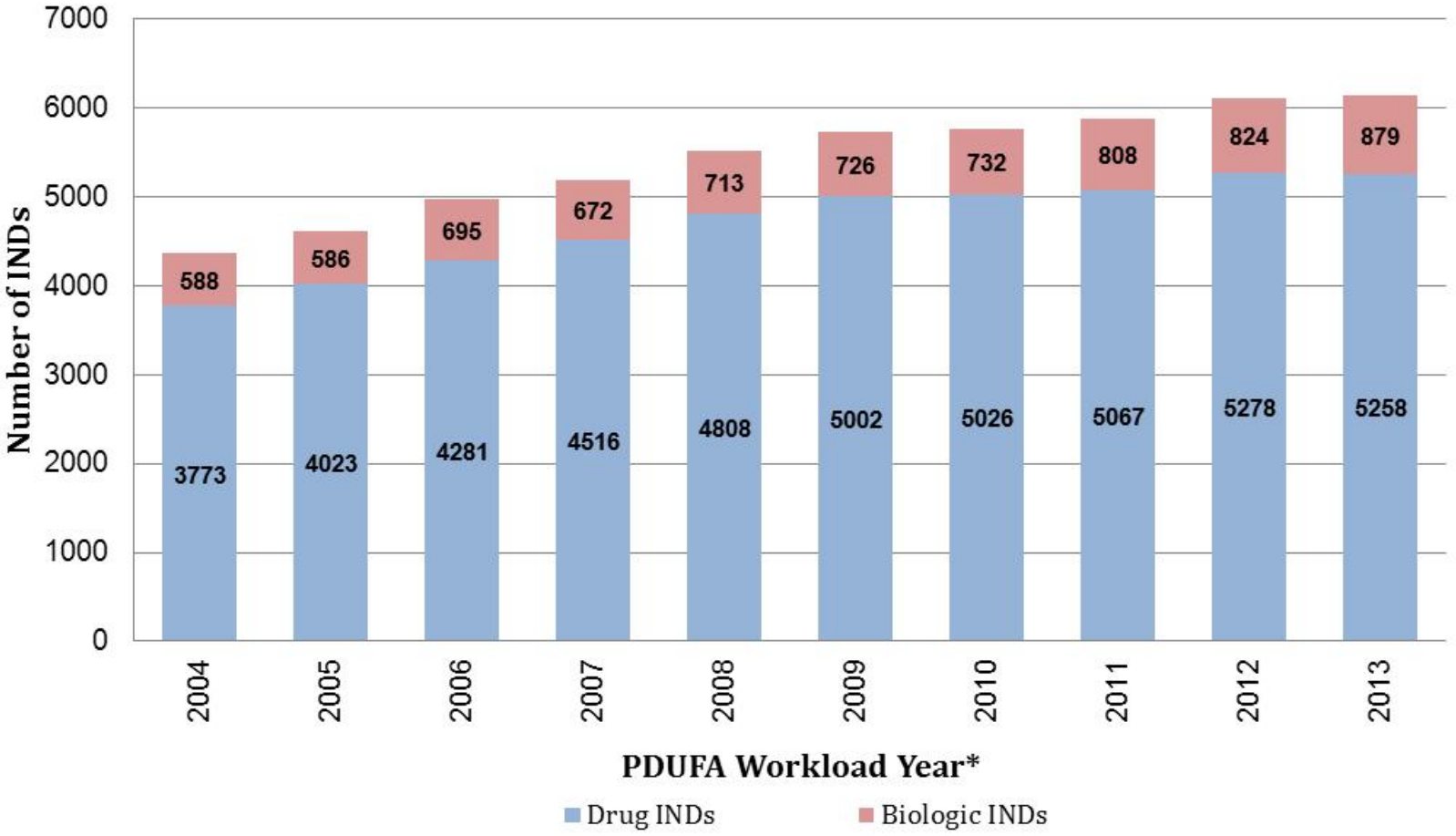
**Potential Performance refers to the level of performance that could potentially be achieved if all the actions currently pending are reviewed within their required goal date.

What About New Drug Approvals?

- The commercial IND pipeline of new drugs under development remains strong
- Through November 30th, CDER received 32 NME applications in CY2013
  - Some are still within the 60-day filing window, subject to RTF
  - A surge of submissions often occurs in December
  - Number of applications filed for review is a major rate-limiting step to the number approved
- To date in CY13 CDER has approved 26 NMEs*
- NME approvals in 2013 include three drugs designated as Breakthrough Therapies that provide much needed new treatment options for patients
- Average first cycle approval rates observed at the end of PDUFA IV have continued into PDUFA V

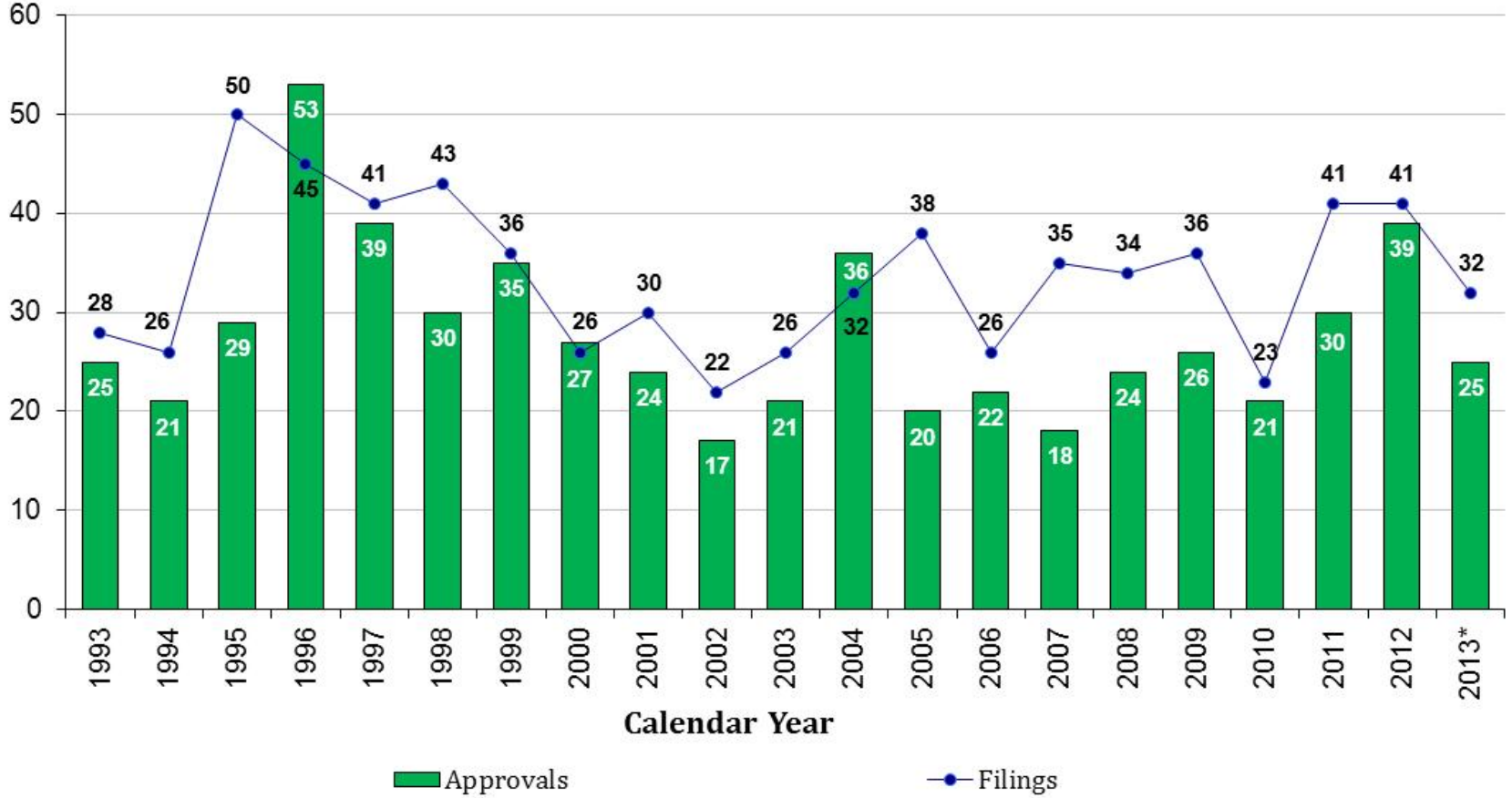
*Total includes sofosbuvir, which was approved 12/6/13, after the data cut-off for subsequent slides.

Commercial INDs With Activity Based On PDUFA Workload Adjuster Data



Data represents 12 month period of July 1st - June 30th

CDER NME NDAs/BLAs† Filings and Approvals



Data as of 11/30/2013

† Multiple applications pertaining to a single new molecular/biologic entity (e.g,., single ingredient and combinations) are only counted once. Therefore, the numbers represented here for FY13 filings are not indicative of workload in the PDUFA V Program.

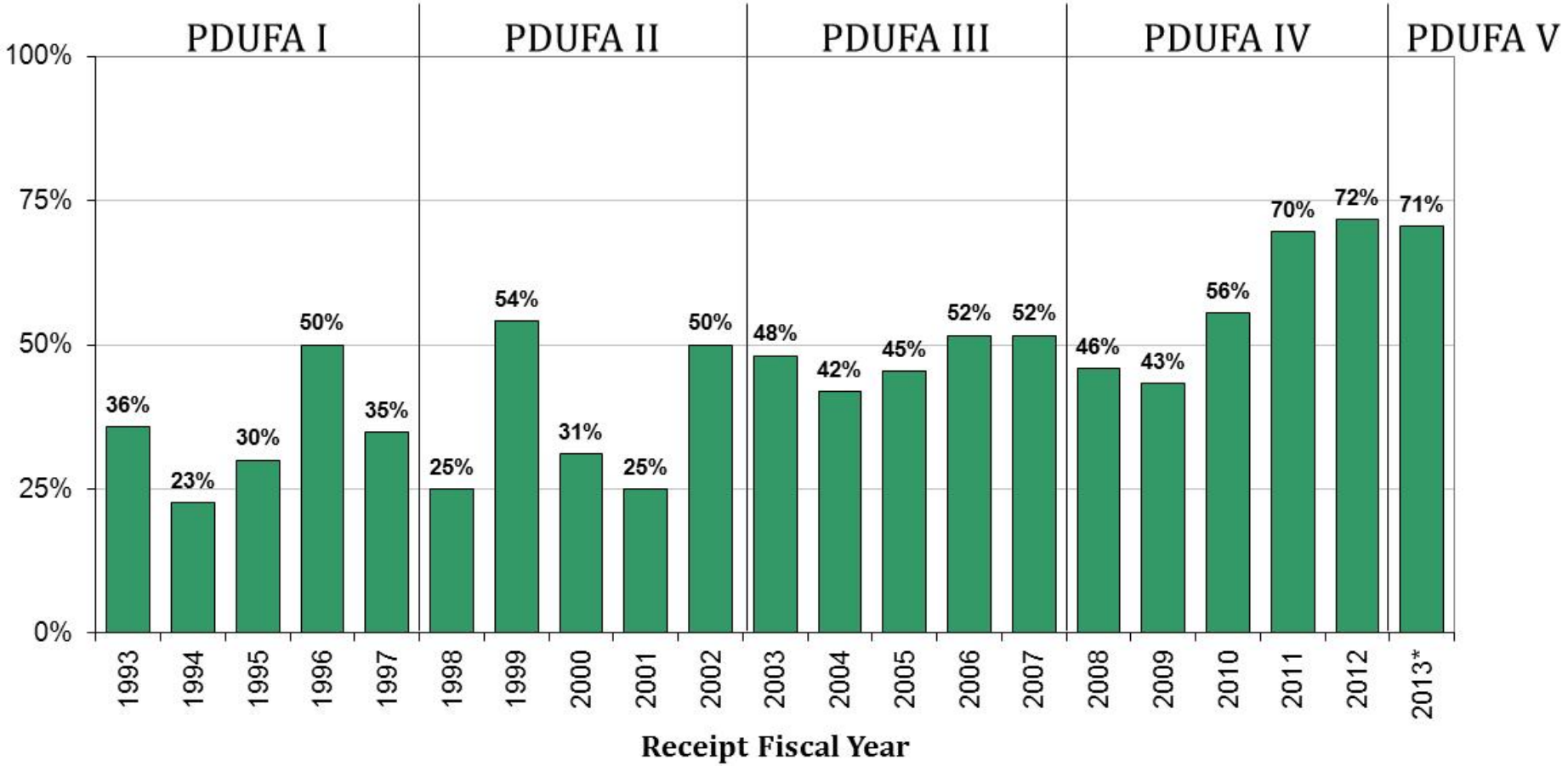
† Original BLAs that do not contain a new active ingredient are excluded

*Since applications are received and filed throughout a calendar year, the filed applications in a given calendar year do not necessarily correspond to an approval in the same calendar year. Certain applications are within their 60-day filing review period and may not be filed upon completion of the review.

Why Fewer NMEs in 2013 vs 2012? Potential Explanations:

- Regression to the mean following an outlier year in 2012?
  - Average NME filings
    - Last 10 years = 33; Last 5 years = 35
    - CY2012 = 41
    - YTD 2013 = 32
  - Average NME Approvals
    - Last 10 years = 26; Last 5 years = 28
    - CY2012 = 39
    - YTD2013 = 26
- CDER became more "conservative" or "risk adverse"
  - First cycle approval rate for NMEs has not significantly changed
- Fewer NME applications with actions due in 2013
  - One time "frame shift" in goal dates for NMEs due to the Program
  - Fewer resubmissions from prior CR cycles

CDER NME NDAs/BLAs†
First Action Approval Rate



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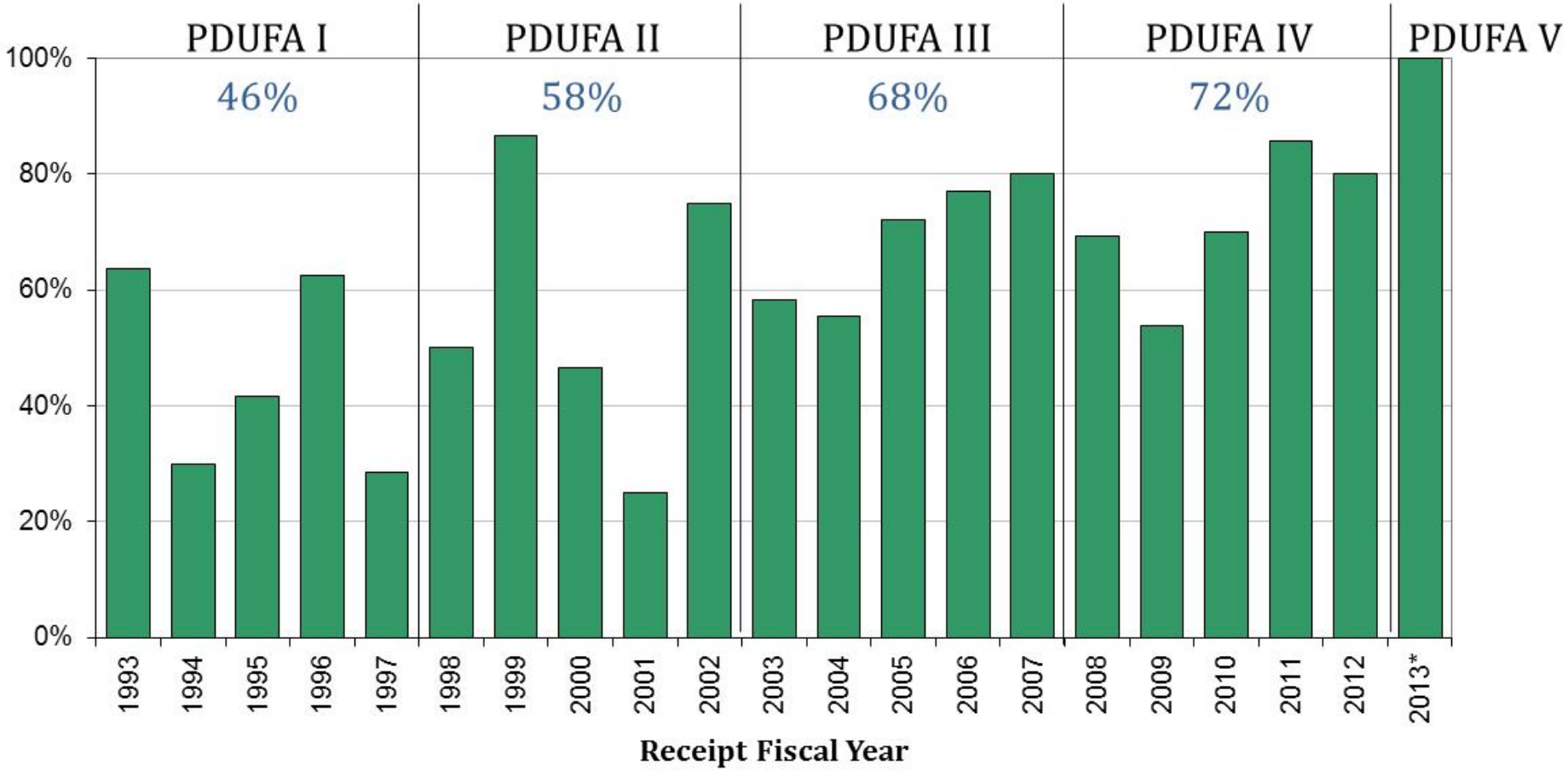
† Original BLAs that do not contain a new active ingredient are excluded

*FY'13 has twenty-four pending applications awaiting first action
FY'13 percentages exclude "Pending" from the denominator

CDER First Action Approval Rates For Priority NME NDAs/BLAs†



Data as of 11/30/2013

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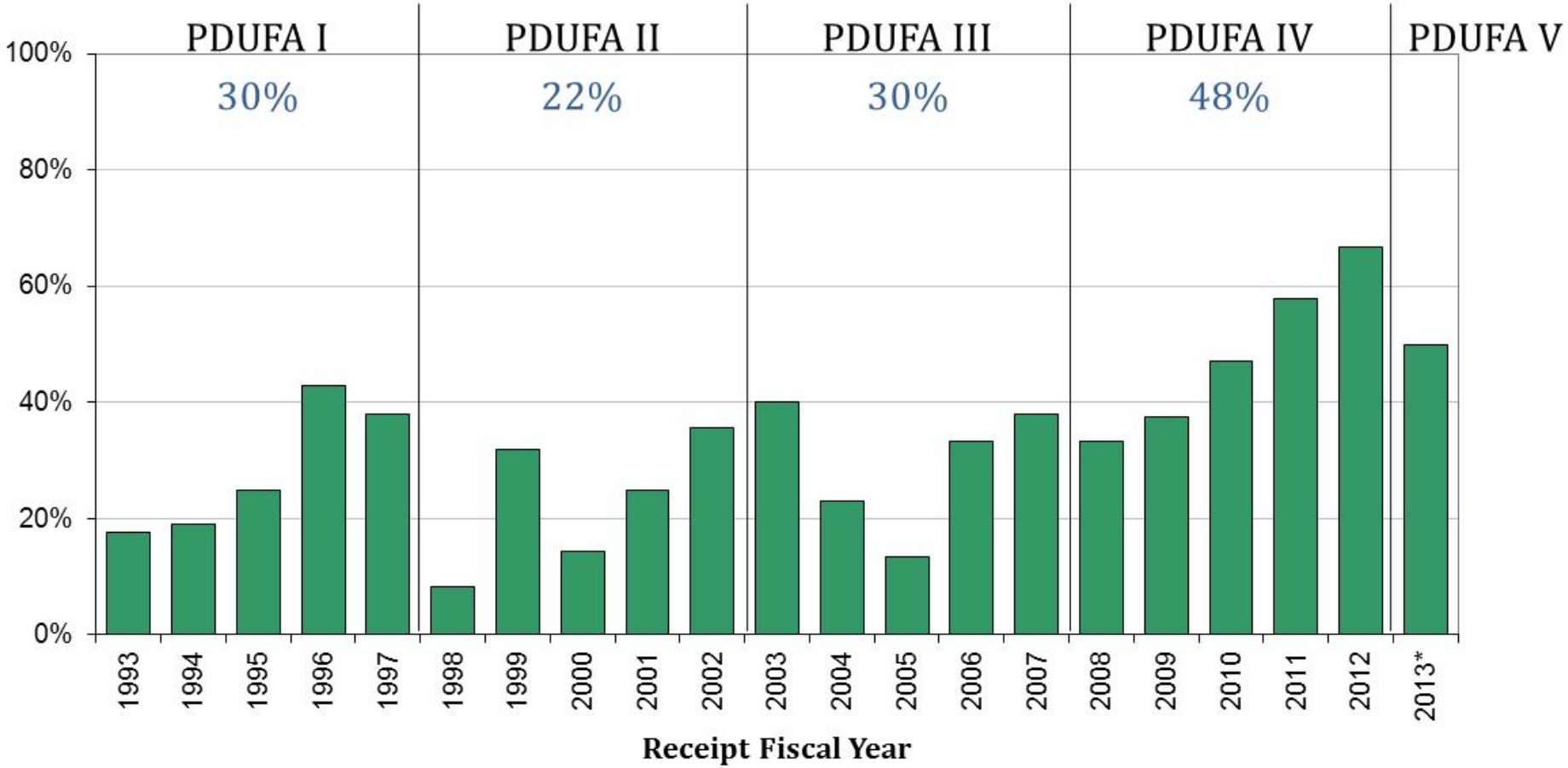
† Original BLAs that do not contain a new active ingredient are excluded

*FY'13 has nine priority pending applications awaiting first action
FY'13 percentages exclude "Pending" from the denominator

CDER First Action Approval Rates For Standard NME NDAs/BLAs†



Data as of 11/30/2013

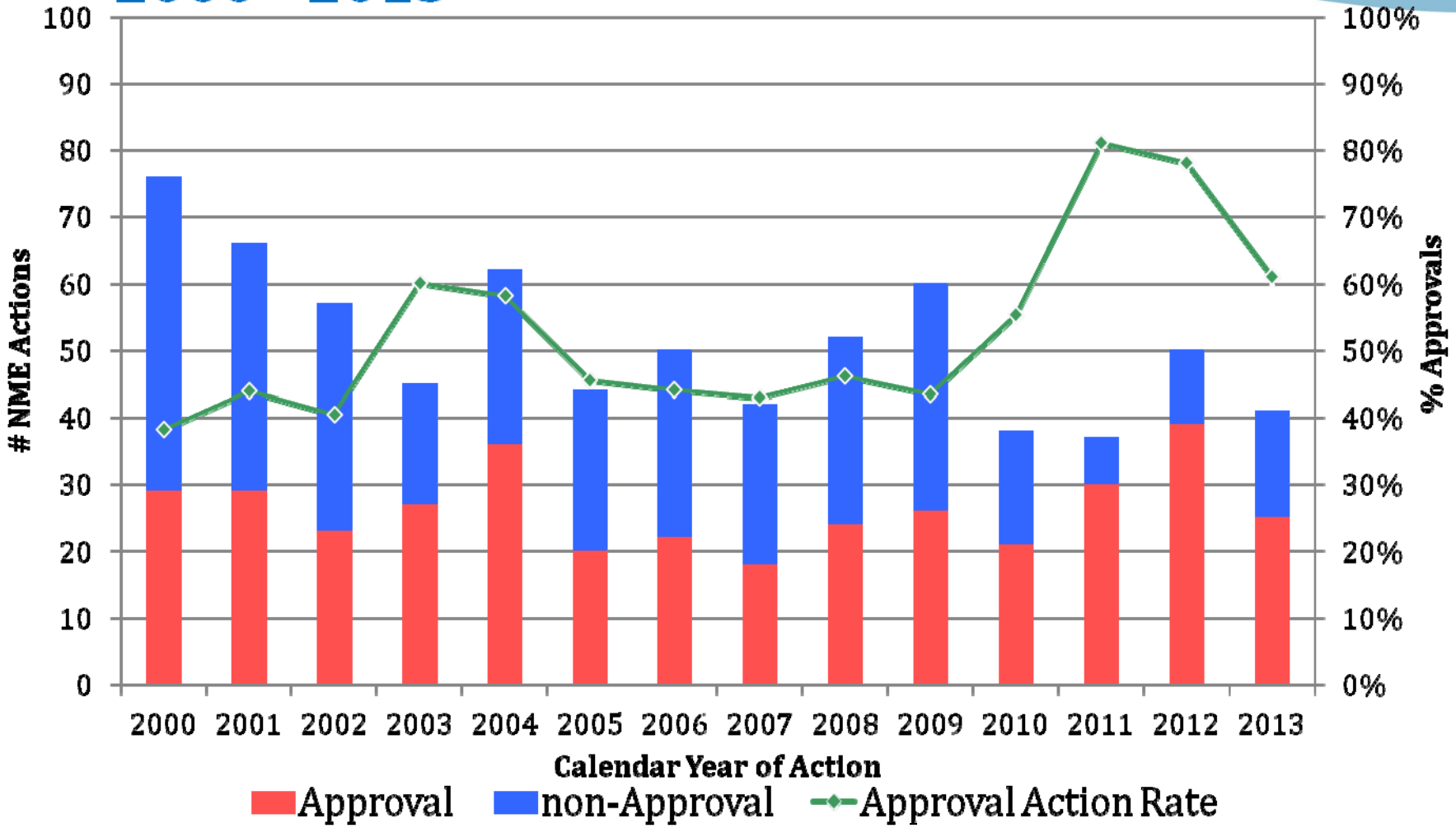
† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers represented here for FY13 filings are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded

*FY'13 has fifteen standard pending applications awaiting first action

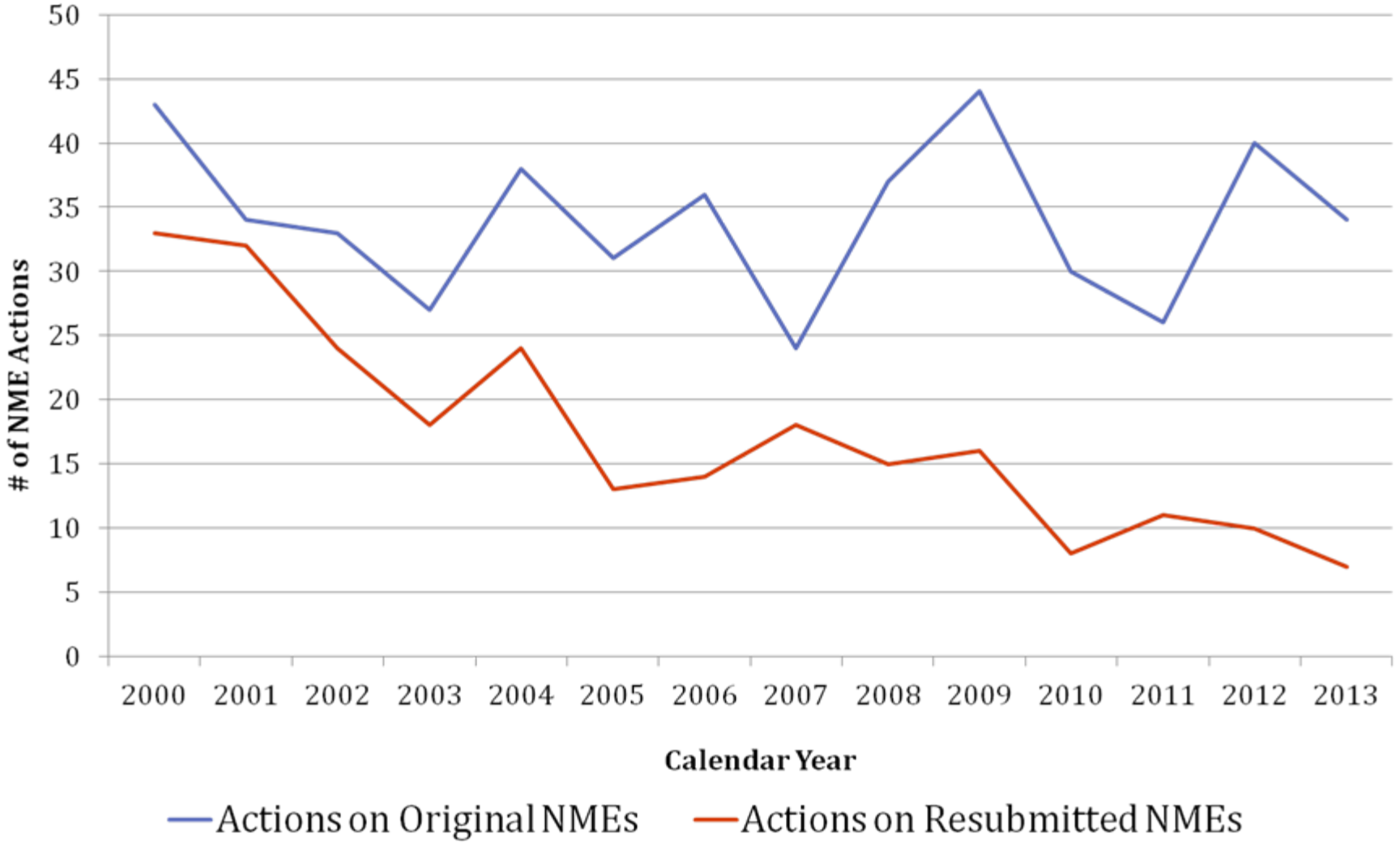
FY'13 percentages exclude "Pending" from the denominator

NME Actions and Approvals 2000 - 2013



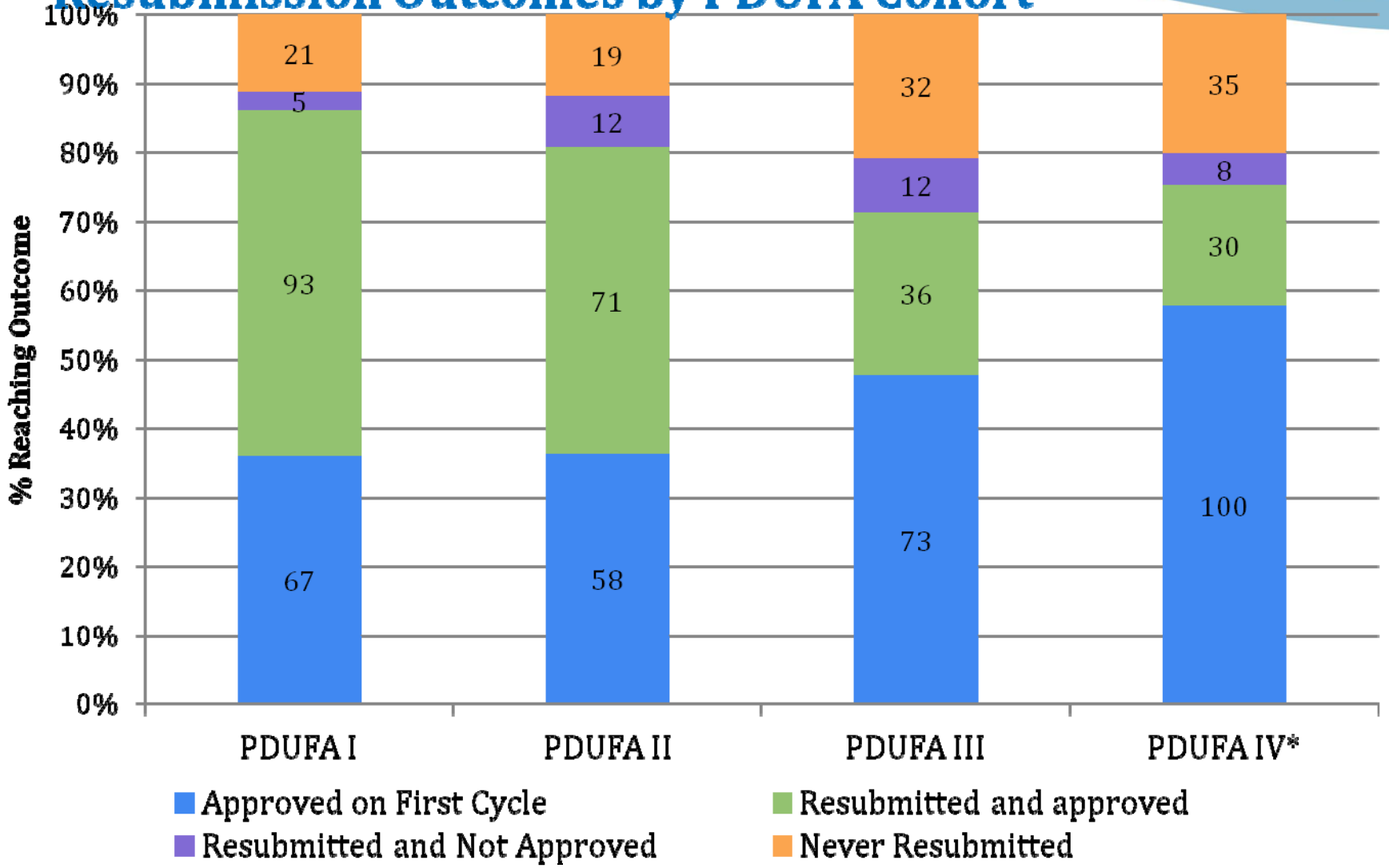
* Data as of 11/30/2013. Includes discrete actions on a given date for active ingredient which, if approved, would constitute a new molecular entity. Actions for original submissions and resubmissions as well as actions for new BLAs are included. Multiple actions which occur on the same date for multiple dosage forms or indications are counted as a single regulatory action.

Original NME and New BLA Actions by Year



* Data as of 11/30/2013.

NME Original Submission and Resubmission Outcomes by PDUFA Cohort



* Some NMEs filed in the latter years of PDUFA IV have not had sufficient time for sponsors to resubmit. These figures are expected to change as this submission cohort 'matures' . Data as of 11/30/2013.

Snapshot of CY 2013
NME NDAs/BLAs† Drug Approvals (1/2)

Trade Name	Met PDUFA Goal Date*	Approved on First Cycle	Priority Approval	Fast Track	First in Class	Approved First in the U.S.	Orphan Drug	Breakthrough Therapy
NESINA								
KYNAMRO								
POMALYST								
KADCYLA								
OSPHENA								
LYMPHOSEEK								
DOTAREM								
TECFIDERA								
INVOKANA								
BREO ELLIPTA								
XOFIGO								
TAFINLAR								
MEKINIST								

Data as of 11/30/2013

† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient an d combinations) are only counted once. Therefore, the numbers represented here for FY13 filings are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded

*A PDUFA Goal Date is marked as met if the NME is acted upon within its approval cycle due date

Snapshot of CY 2013
NME NDAs/BLAs† Drug Approvals (2/2)

Trade Name	Met PDUFA Goal Date*	Approved on First Cycle	Priority Approval	Fast Track	First in Class	Approved First in the U.S.	Orphan Drug	Breakthrough Therapy
GILOTRIF								
TIVICAY								
BRINTELLIX								
DUAVEE								
ADEMPAS								
OPSUMIT								
VIZAMYL								
GAZYVA								
APITOM								
IMBRUVICA								
LUZU								
OLYSIO								

Data as of 11/30/2013

† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers represented here for FY13 filings are not indicative of workload in the PDUFA V Program.

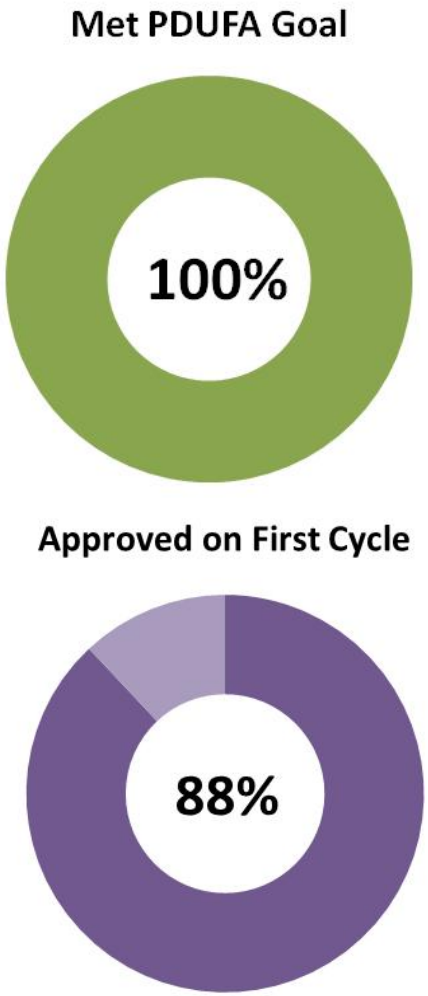
† Original BLAs that do not contain a new active ingredient are excluded

* A PDUFA Goal Date is marked as met if the NME is acted upon within its approval cycle due date

In CY 2013, CDER Continued To Ensure The Efficiency Of First Cycle Review

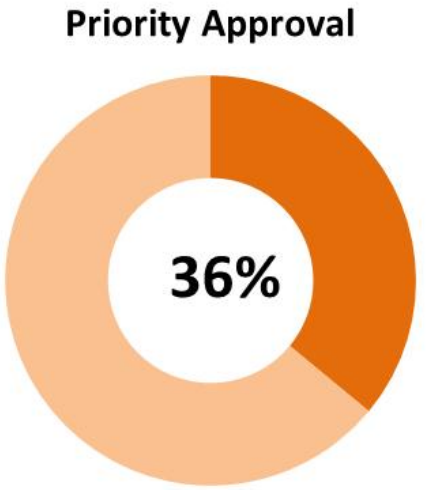
- All novel drugs approved to date in CY13 met their PDUFA goal dates for the approval review cycle

- 22 out of 25 (88%) novel drugs approved to date in CY13 were approved in the first review cycle

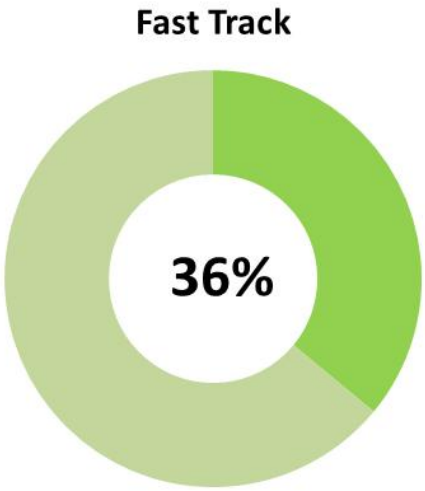


CDER Ensures That Novel Drugs Receive Expedited Review

- 9 out of 25 (36%) novel drugs approved to date in CY13 were approved under Priority Review

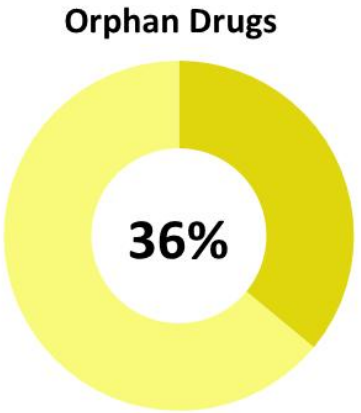


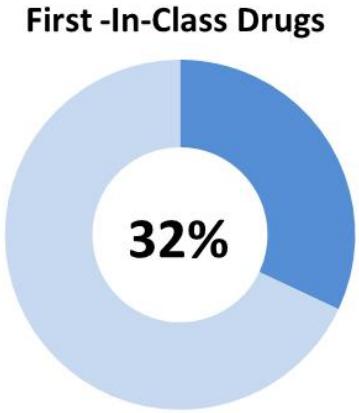
- 9 out of 25 (36%) novel drugs approved to date in CY13 received Fast Track designation

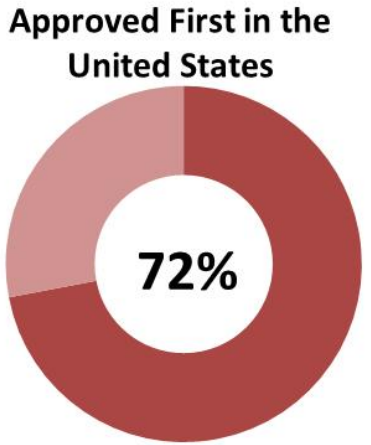


2013 Continues A Strong Track Record For Drug Innovation In The U.S.

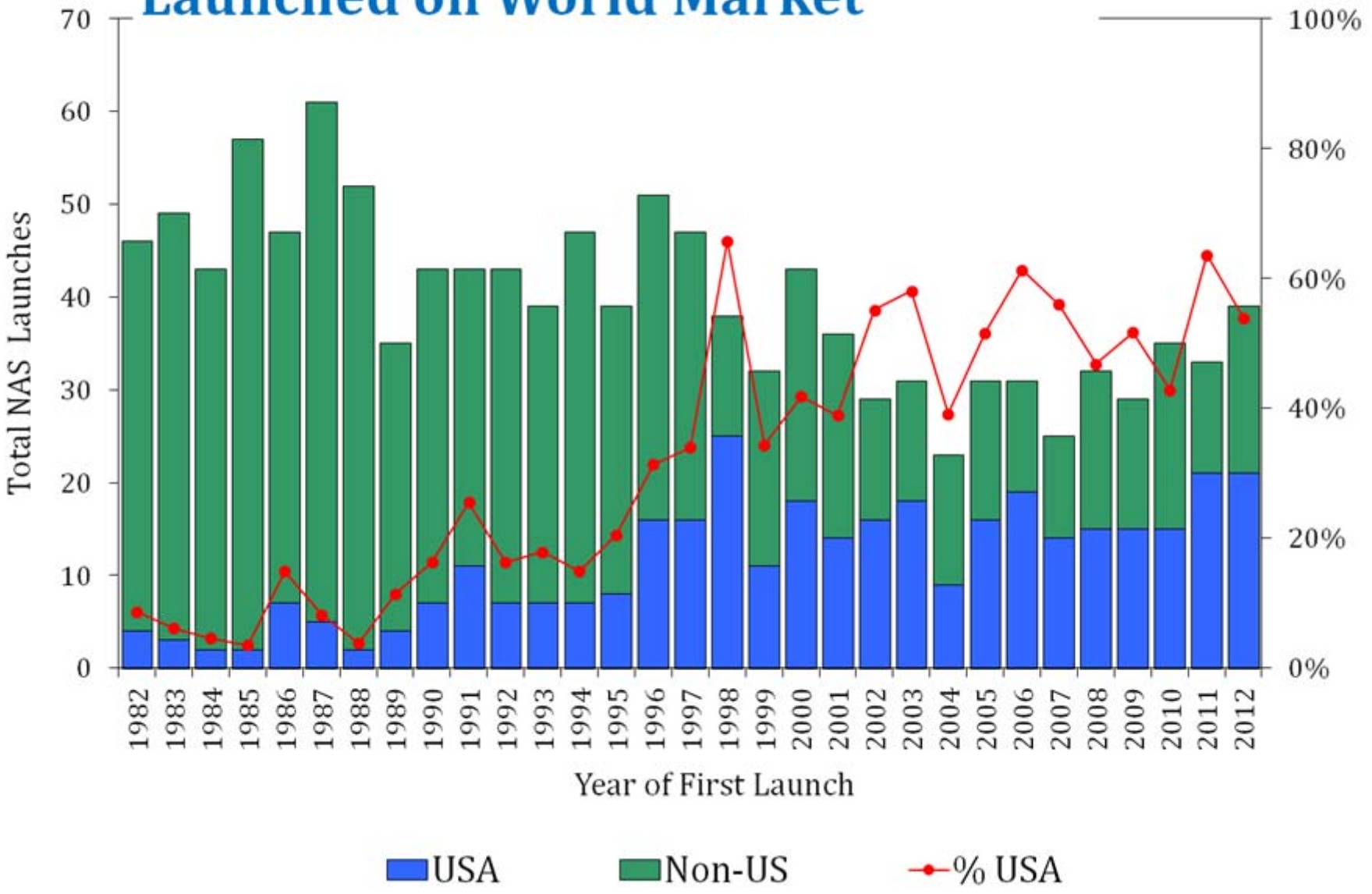
- More than a third (36%) of novel drugs approved to date in CY13 are for rare diseases
- Nearly one out of three (32%) of novel drugs approved to date in CY13 are the first in their class
- Approximately three-quarters (72%) of novel drugs approved to date in CY13 were first approved in the U.S.



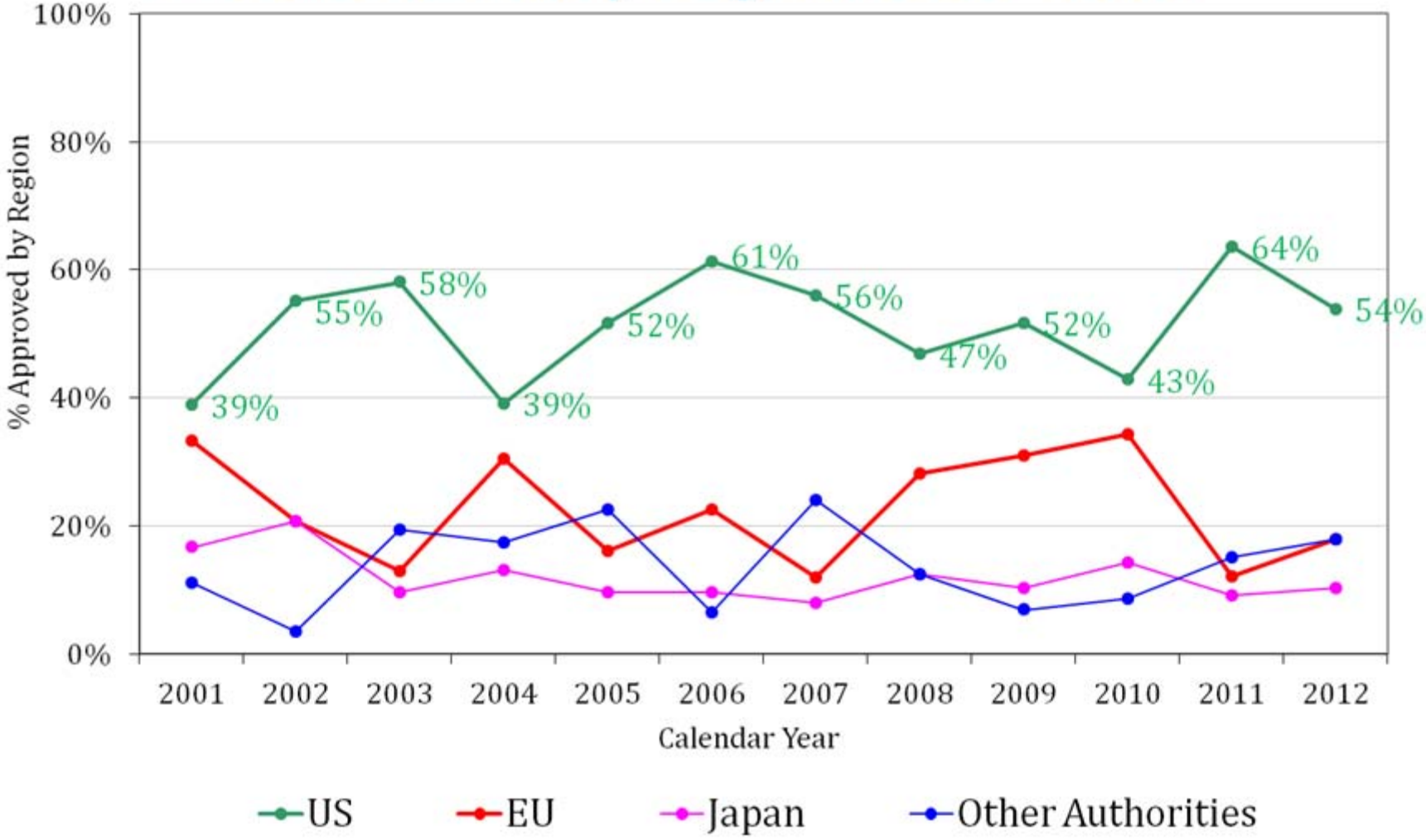




USA Share of New Active Substances Launched on World Market

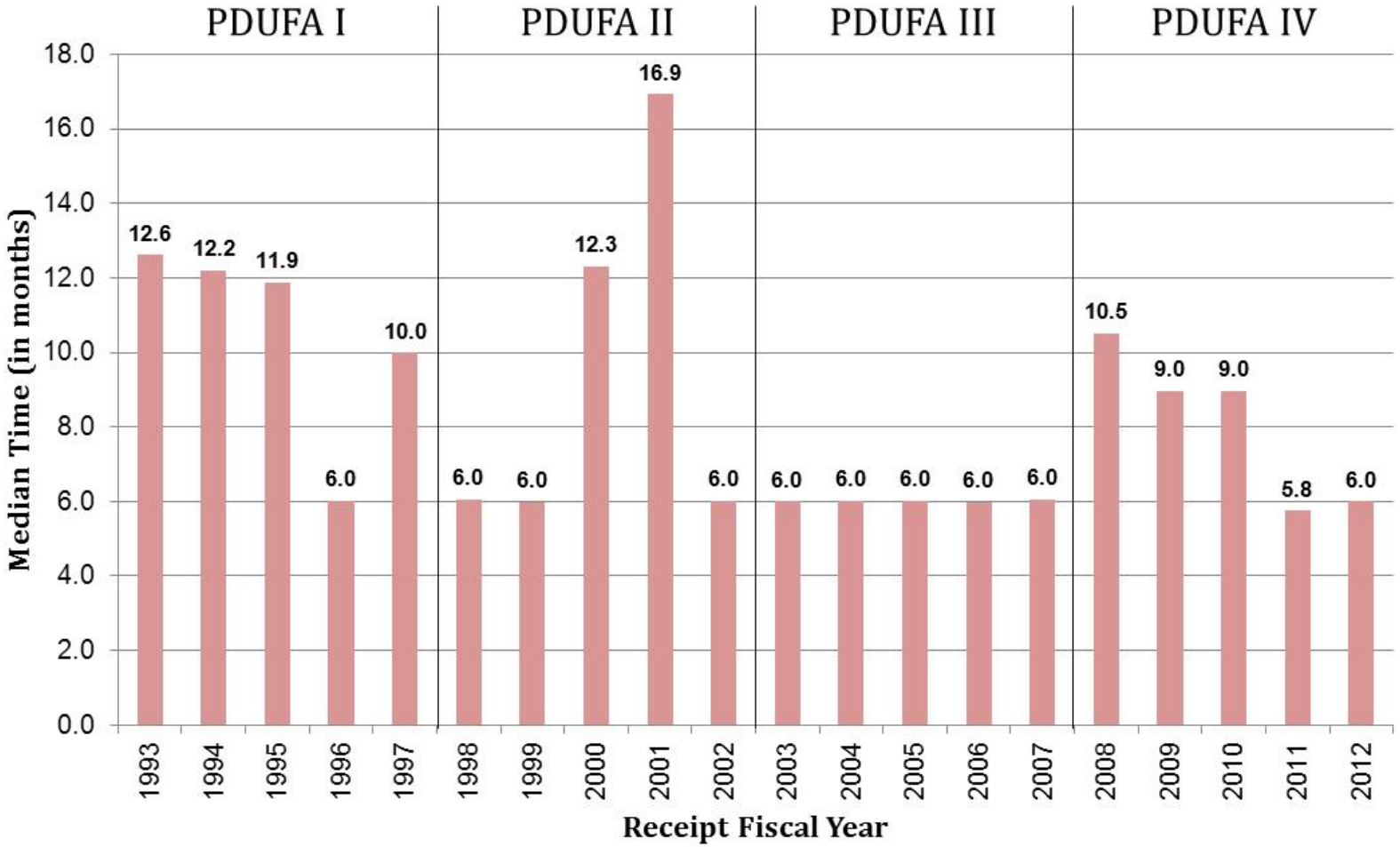


Global New Active Substances First Launches by Region 2001 - 2012



Source: *Scrip Magazine* (2001 - 2006), *Pharmaprojects/Citeline* **Pharma R&D Annual Review** (2007 - 2013)

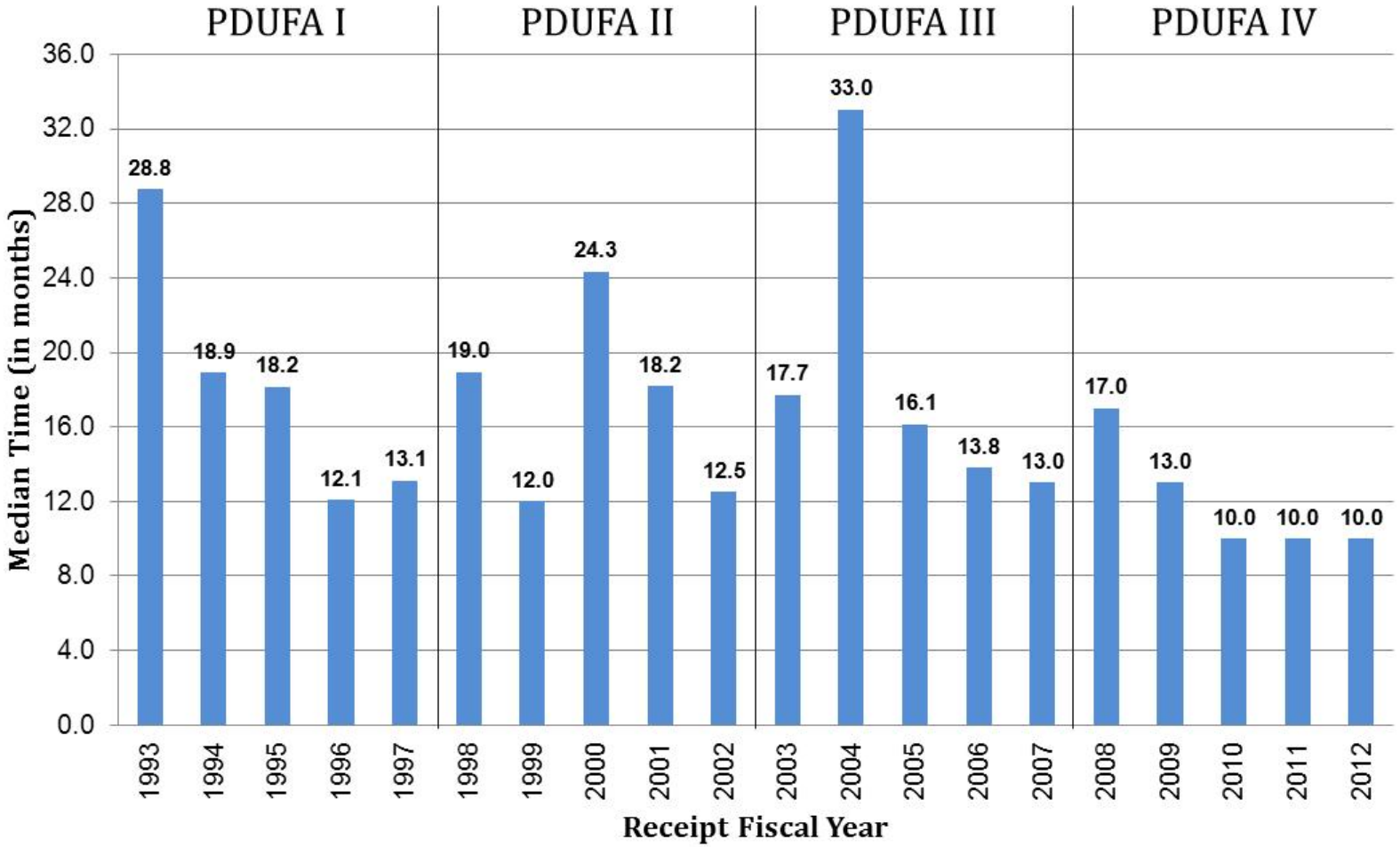
CDER Priority NME NDAs/BLAs† Median Total Time to Approval



Data as of 9/30/2013

† Original BLAs that do not contain a new active ingredient are excluded

CDER Standard NME NDA/BLAs† Median Total Time to Approval



Data as of 9/30/2013

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Selected PDUFA V/FDASIA Programs That Impact Drug Development and Review

Review "Program" for NME NDAs and Original BLAs

Goal

- "Improve the efficiency and effectiveness of the first cycle review process and decrease the number of review cycles necessary for approval, ensuring that patients have timely access to safe, effective, and high quality new drugs and biologics." (PDUFA V Goals Letter)

Concept

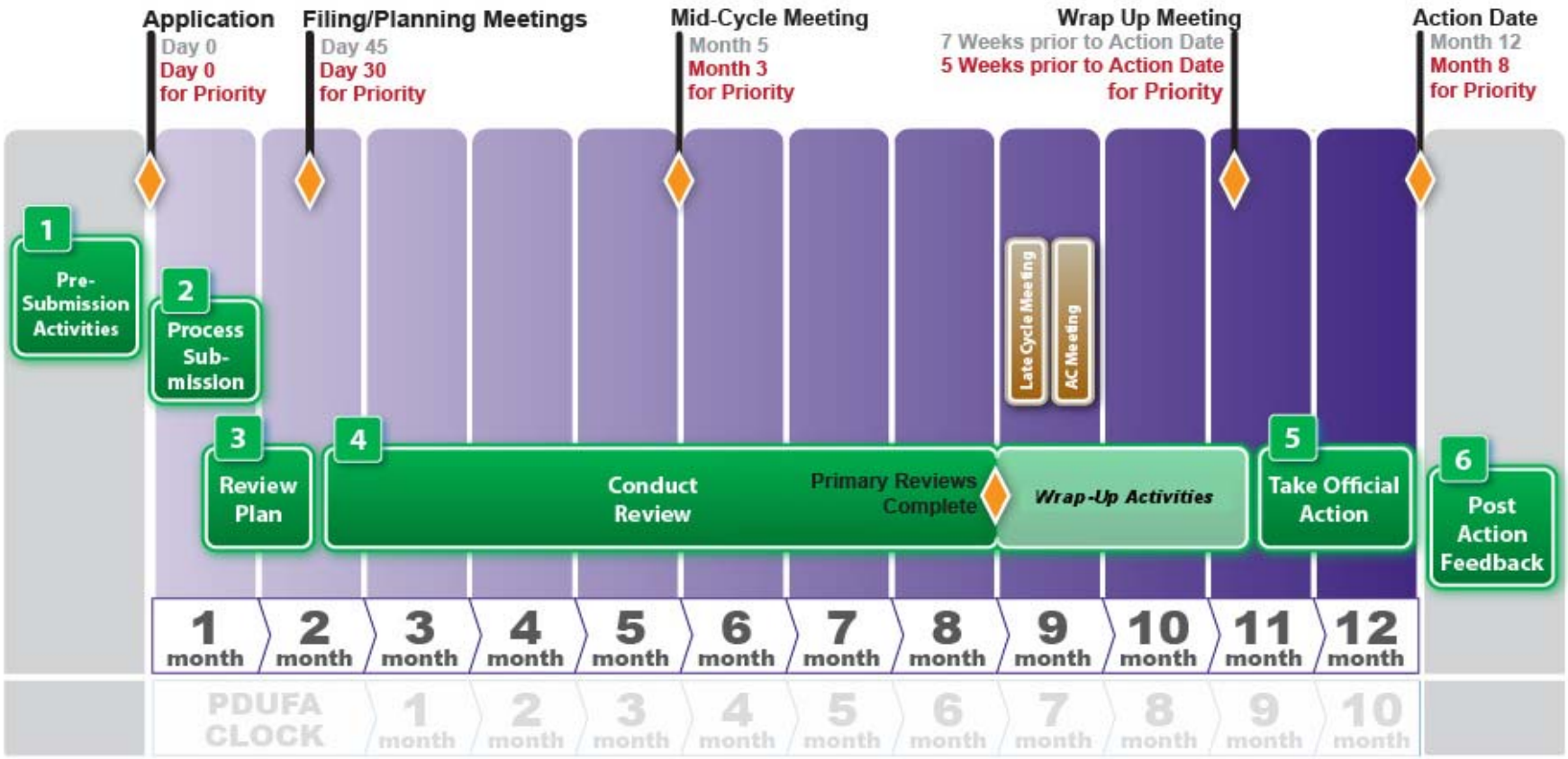
- Better planning before application submission, submission of complete applications, improved communication and transparency between applicant and review team during review, and additional review time will improve the efficiency of the first review cycle, which may decrease the number of additional review cycles prior to approval.

Review "Program" for NME NDAs and Original BLAs

Components

- Pre-submission meeting strongly encouraged
- Complete application at time of submission; incomplete subject to RTF
- 60-day filing review period "off the clock"
- 74-Day Letter
  - Planned review timeline, planned date of internal mid-cycle meeting, preliminary plans on need for AC meeting, early communication of deficiencies/information requests
- Mid-Cycle Communication
  - Within 2 weeks of internal mid-cycle meeting
  - Communication of significant issues identified to date/information requests, preliminary thinking on risk management/REMS, proposed dates for late-cycle meeting, updates on AC plans
- Discipline review letters
  - Summarize preliminary findings/deficiencies by discipline
- Late-cycle meeting (LCM)
  - Focus on information sharing, planning for AC, and planning for the remainder of review

Sample "Program" Review Timeline – Standard Application



Review "Program" Implementation

- All NME NDAs, original BLAs, and resubmissions following RTF received from 10/1/12 – 9/30/17
- Program has been running smoothly to date
- Independent expert contractor hired to assess the program in real time
  - Interim report to be published for comment by March 31, 2015
  - Final report to be published for comment by December 31, 2016
- Too early to assess whether the program is meeting its goals
  - Early feedback from the contractor's interviews with FDA staff and sponsors has generally been positive
  - Some concern from FDA staff about additional workload without additional resources (the Program was negotiated as "resource neutral") and timeline challenges for expedited reviews

FY 2013 Cumulative Activity in the Program

	Q1 FY2013 (12/31/12)	Q2 FY2013 (3/31/13)	Q3 FY2013 (6/30/13)	Q4 FY2013 (9/30/13)
Pre-Submission Meetings	17	24	33	42
Applications Received	18 14 NDAs 4 BLAs	27 18 NDAs 9 BLAs	42 26 NDAs 16 BLAs	54 33 NDAs 21 BLAs
Refuse-to-File Actions	2	2	2	2
Mid-Cycle Communications	0	7	20	33
Discipline Review letters	0	0	3	5
Late-Cycle Meetings	0	0	4	17
First Cycle Actions	0 0 APs 0 CRs 0 WFs	0 0 APs 0 CRs 0 WFs	1 1 AP 0 CRs 0 WFs	6 4 APs 0 CRs 2 WFs
Post-Action Interviews	0 0 FDA 0 Applicant	0 0 FDA 0 Applicant	2 1 FDA 1 Applicant	6 3 FDA 3 Applicant

AP = Approval
CR = Complete Response
WF = Withdrawal after Filing

Breakthrough Therapies

- FDASIA program to expedite development and approval of new drugs intended to treat a serious condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies
- FDASIA endorsed and extended FDA's long-standing policy of expediting promising new drugs for serious and life-threatening conditions
- Draft guidance "Expedited Programs for Serious Conditions––Drugs and Biologics" issued June 2013
  - Final guidance is currently being drafted based on feedback and comments

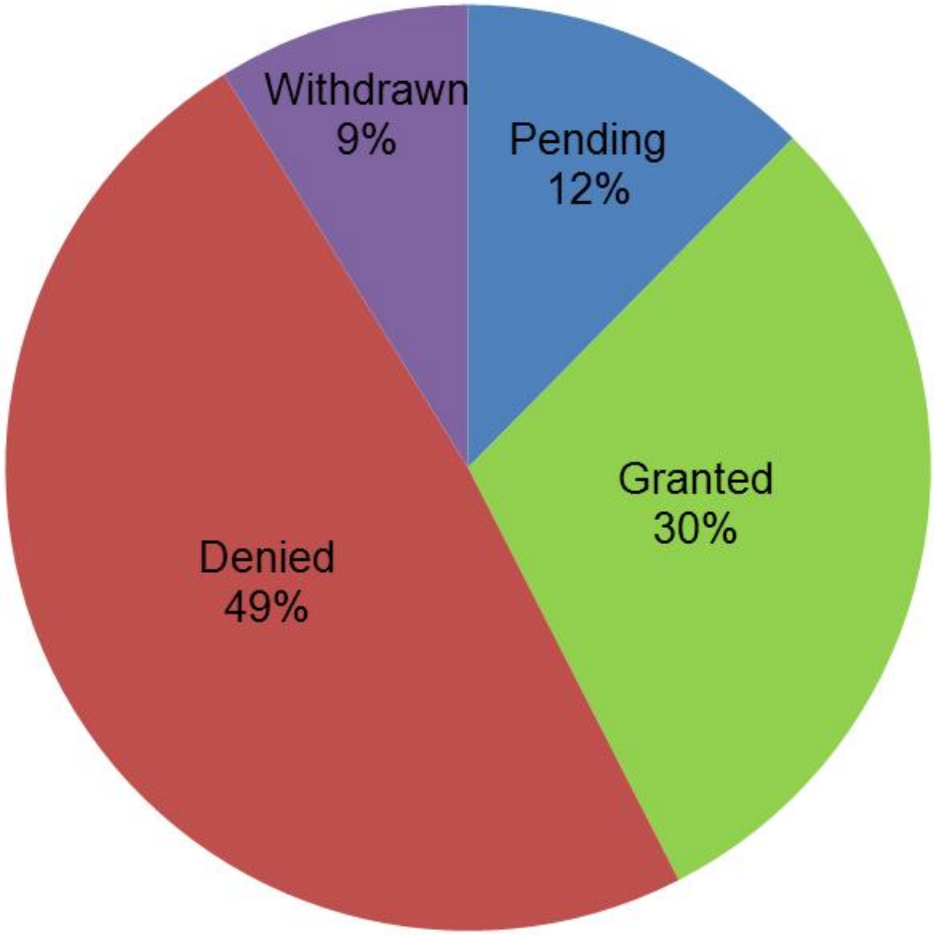
Breakthrough Therapies: Lessons Learned To Date

- Statutory criteria are subjective; require judgment by FDA
  - All BT requests in CDER are reviewed by the Medical Policy Council to ensure consistency of standards and approach
- Some designated drugs have been late in development; in some cases the marketing application already submitted
  - Main focus of program is on identifying drugs early in development; shift toward earlier stages of development expected as program matures
- Clinical development often NOT the rate-limiting step
  - Manufacturing development and scale-up must be accelerated
- Program commitments are resource intensive for FDA
  - Number of requests and designations have exceeded expectations
  - We are working to minimize adverse impact on other programs

Breakthrough Therapies: Lessons Learned (2)

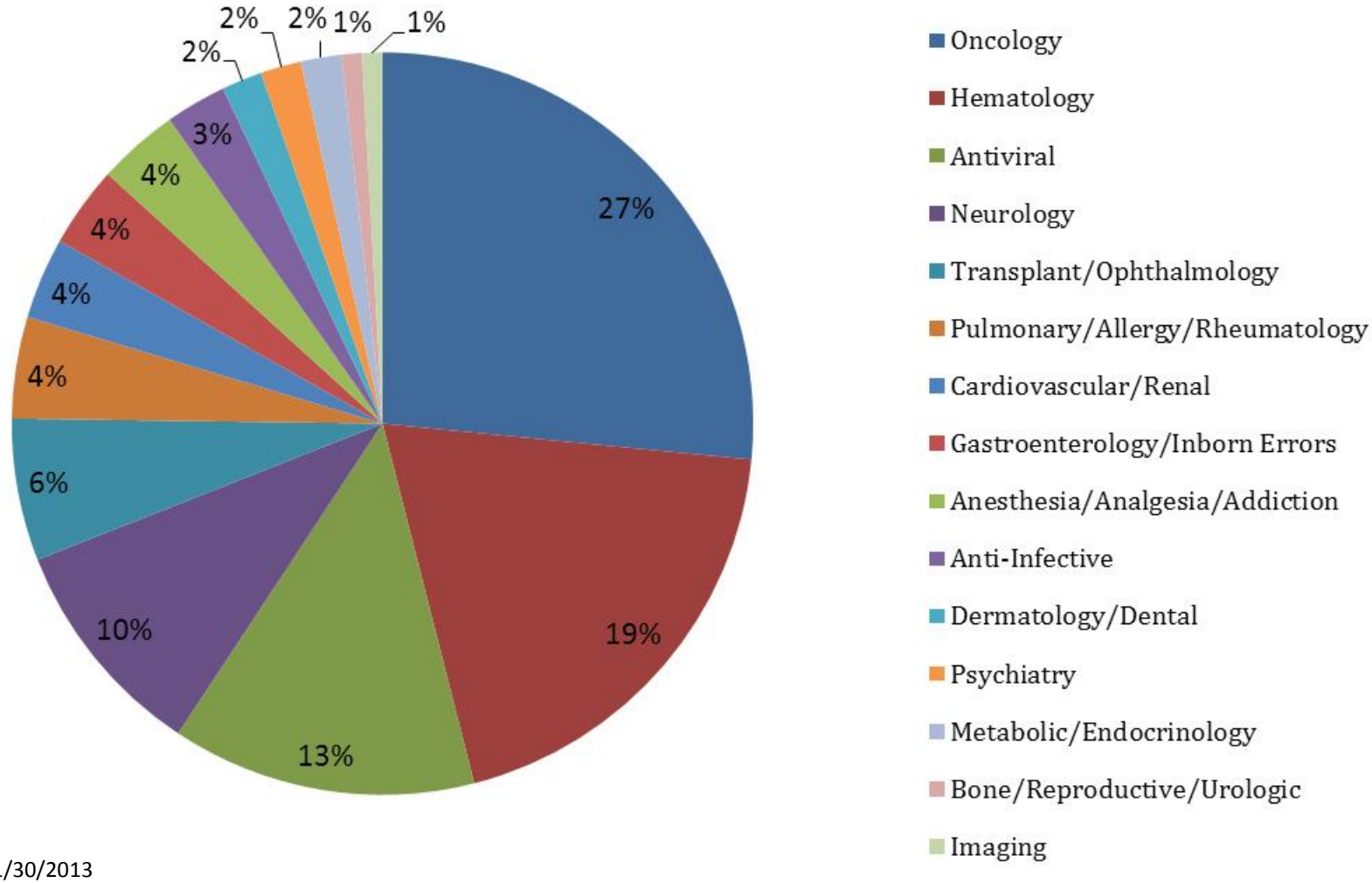
- BT designations generally occur under an IND
  - FDA is prohibited from discussing details of decisions and many sponsors do not make public announcements
  - Lack of transparency adds to confusion regarding standards
- Common reasons for denial of BT requests
  - Evidence does not include clinical data
  - Evidence is too preliminary to be considered reliable; e.g., very small number of patients treated, anecdotal case reports
  - Failure to demonstrate "substantial" improvement over available therapy
  - Reliance on a novel biomarker or surrogate endpoint without sufficient evidence to support benefit to patient
  - Post-hoc analyses of failed studies that identify a subset that may benefit

Current Status of 113 CDER Breakthrough Therapy Requests



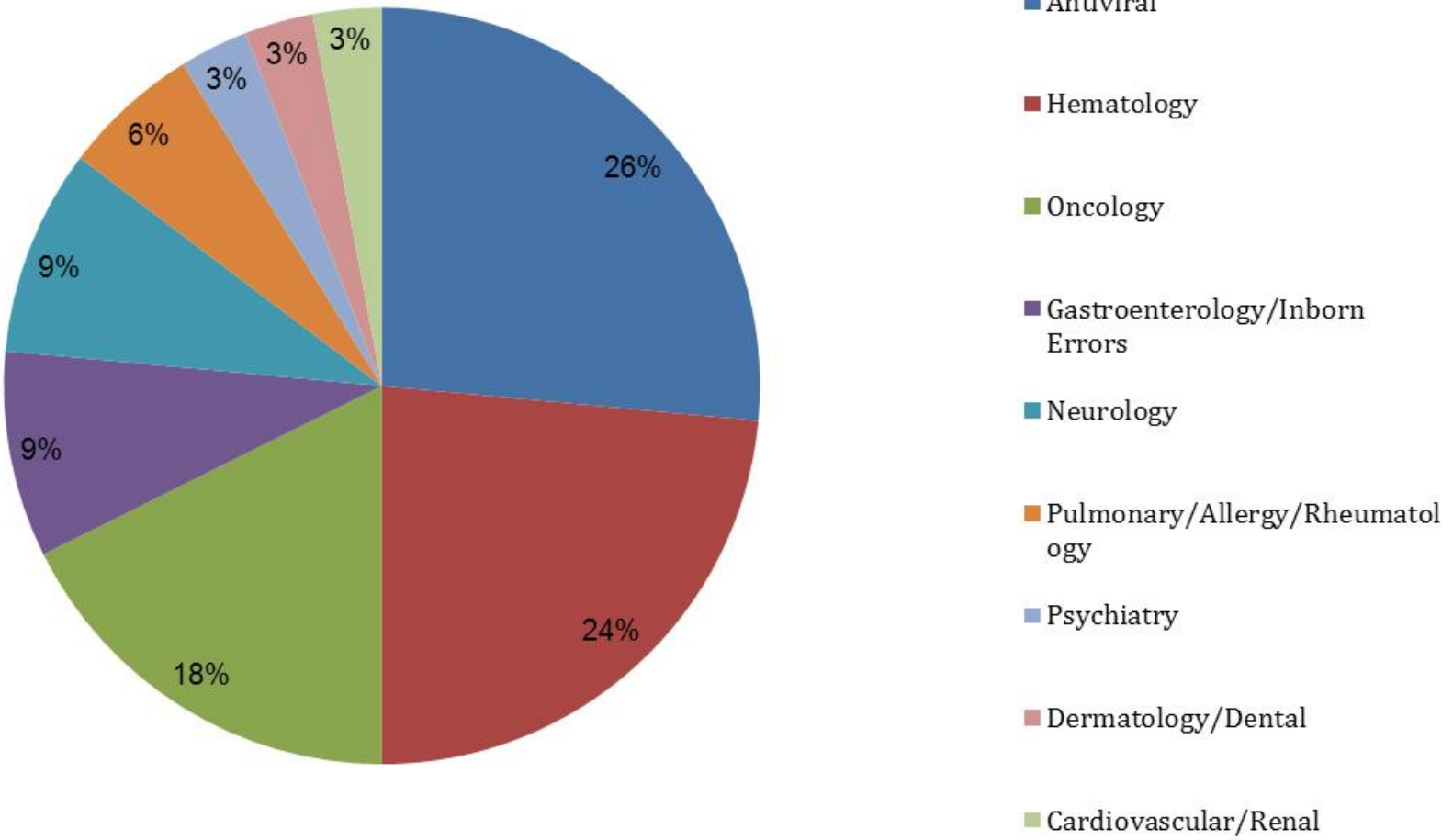
Data as of 11/30/2013

CDER Breakthrough Therapy Requests by Division



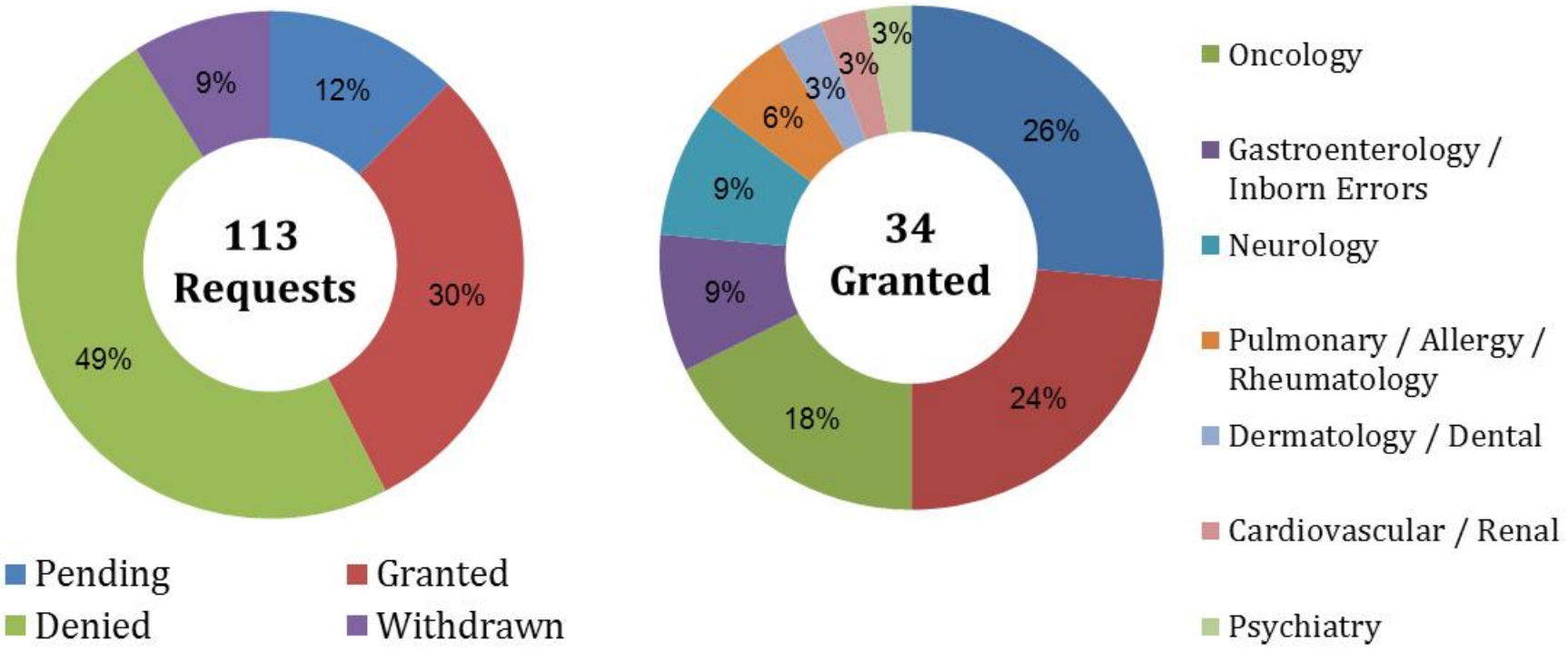
Data as of 11/30/2013

CDER Breakthrough Therapy Requests **Granted** by Division



Data as of 11/30/2013

CDER Has Granted 34 Breakthrough Therapy Designations Since Inception



Data as of 11/30/2013

Update on PMCs/PMRs: Urban Legend versus Data

PMCs/PMRs – What are the Facts?

- Urban legend – sponsors don't take PMCs and PMRs seriously and FDA is lax in following up on these studies
  - Two recently published analyses by Fain, et al[1] and Moore, et al[2] have raised questions about sponsor compliance and FDA action
- Reality – Available data show that sponsors are generally meeting their obligations under PMCs and PMRs
- Common misperception that "pending" is a pejorative term when applied to PMCs/PMRs
  - Pending ≠ delayed
  - Pending means a study has not yet started, but is on schedule
- Delayed does not necessarily mean lack of effort by sponsor
  - Legitimate delays sometime occur in starting/executing trials despite a sponsor's best efforts

[1] *JAMA.* 2013;310(2):202-204. doi:10.1001/jama.2013.7900. [2] *JAMA Intern Med.* 2013; doi: 10.1001/jamainternmed.2013.11813

Annual FR Notice Data: FDAAA PMRs

Status Category	2007	2008	2009	2010	2011	2012[1]
Open Statuses	Number of FDAAA Safety Postmarketing Requirements					
Pending	0	42	120	207	271	253 (49%)
Ongoing	0	4	28	50	64	96 (19%)
Submitted	0	0	5	16	33	55 (11%)
Delayed	0	0	0	6	19	38 (7%)[2]
Terminated	0	0	0	0	0	0 (0%)
Closed Statuses						
Fulfilled	0	0[4]	0[3]	0[3]	0[3]	59 (12%)
Released	n/a	n/a	n/a	n/a	n/a	12 (2%)
TOTAL	0	46	153	279	387	513

[1] Preliminary data as of September 30, 2012. Under review for quality control.
[2] Of the 38 Delayed FDAAA PMRs as of September 30, 2012, 34% (13/38) have since been completed (Fulfilled or Submitted) and 58% (22/38) are Ongoing with revised timelines acknowledged by the FDA.
[3] Annual FR notices do not report number of Fulfilled FDAAA PMRs only total number of Fulfilled PMRs/PMCs

PMR/PMC Backlog by Annual Review Cycle[1]

PMR/PMC Status	#After 1st Review[2]	#After 2nd Review	#After 3rd Review	#After 4th Review	#After 5th Review [3,4]
Pending	208 (14%)	114 (7%)	93 (6%)	77 (5%)	**52 (3%)**
Ongoing	212 (14%)	156 (10%)	132 (8%)	106 (7%)	**71 (5%)**
Submitted	565 (36%)	366 (24%)	197 (13%)	113 (7%)	**77 (5%)**
Delayed	225 (15%)	264 (17%)	223 (14%)	199 (13%)	**172 (11%)**
Terminated	16 (1%)	13 (<1%)	13 (<1%)	10 (<1%)	**11 (<1%)**
Fulfilled	209 (14%)	483 (31%)	701 (45%)	827 (53%)	**900 (58%)**
Released	47 (3%)	146 (9%)	191 (13%)	222 (14%)	**272 (17%)**
Undetermined	39 (2%)	9 (<1%)	0	0	**0**
Not Available	30 (1%)	0	0	0	**0**
Total	1,551	1,551	1,550	1554	**1555**

[1] Annual review and reporting required under FDAAA 2007.
[2] Reflects data following review and correction of the actual statuses of the original backlog cohort of PMRs and PMCs
[3] Preliminary data as of September 30, 2012. Under review for quality control.
[4] FY 2012 data are for CDER applications only, does not include CBER data.

PMRs/PMCs for Novel Drugs Approved in 2008[1]

PMR/PMC Type	Pending	Ongoing	Delayed	Submitted	Released	Fulfilled[3]	Total
PMC -Efficacy	0	0	0	1	0	4	5
PMC -Other	0	1	2	2	7	10	22
PMR -Accelerated Approval	0	0	0	0	0	3	3
PMR - PREA (Deferred Pediatric)	9	5	4	0	3	2	23
PMR – FDAAA Safety	0	8	6[2]	16	4	11	45
TOTAL	9	14	12	19	14	30	98

[1] Preliminary data as of September 30, 2013. Under review for quality control.
[2] Of the 6 Delayed FDAAA PMRs, all are currently underway. One is projected to meet the original final report due date; 3 are progressing according to a revised schedule acknowledged by the FDA; and 2 studies are open but the applicant has requested release and proposed alternative studies to fulfill the PMRs.
[3] 73% of the 2008 cohort of PMR/PMCs expected to be completed by 9/30/2013 were completed. **For the FDAAA PMRs 84% were completed.**

CDER New Drug Review: 2013 Summary

- CDER is meeting or exceeding nearly all PDUFA application review goals
- 26 NME approvals to date this CY is in line with historical averages and mainly reflective of a decrease in the number of NME applications with PDUFA goals in CY2013
- CDER has successfully implemented the NME Program; too early to assess impact on first cycle review performance
- Breakthrough therapy program is very popular and the number of designated drugs has exceeded expectations
  - 3 BT-designated drugs have been approved to date
- Despite urban legend; data show that sponsors are generally completing PMCs/PMRs in a timely manner

Thank You!